REMARKS

Claims 1-72 were presented for examination. Restriction was required between Groups I-IV. The applicant appreciates the Examiner's modification of that restriction requirement; as a result of the modification, Groups III and IV were rejoined. Pursuant to this restriction, claims 1-30 have been withdrawn from consideration, and claims 31-72 were examined, and were rejected.

The applicant appreciates the Examiner's diligent review of the specification and claims, which identified a number of items for correction. Each of the recommended corrections has been made by the present amendment. In addition, the applicant has corrected other errors noted during the preparation of this response, including obvious typographical errors, and misspelling of the names of an author of a reference. These amendments add no new matter.

Claims 35, 43, 49, 56, and 66 were amended to include the limitations of claim 1, since claim 1 has been withdrawn. Claims 36 and 57 were amended to present the reaction more clearly by making the arrow long enough to accommodate all of the text above it. Claim 45 was amended per the Examiner's suggestion to recite a "kit for assaying...." Claims 50 and 68 were amended to note that either AMP or P_i can be used as an indicator of the progress of the reaction, since it produces both species. This possibility is recognized, for example, in paragraph [0008].

Claims 47 and 71 were amended by deleting the phrase "if sodium (lithium) ions are not present." The reaction described in the claims is used to detect product to determine whether the ions to be detected are present, thus it comprises the "means for assessing the product formed", regardless of whether the ions are present. Claims 60 and 69 were amended to correct typographical errors noted by the Examiner.

None of these amendments add new matter.

The Examiner's comments have been carefully considered, and the following remarks are offered in response. The applicant respectfully requests reconsideration of the claims as amended herein, in view of these remarks.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 31-72 were rejected for allegedly failing to comply with the enablement requirement. Several specific items were mentioned under this heading, and are addressed in the order the Examiner presented them.

First, the Examiner asks for clarification of the terms "intra-assay", "Inter-assay" and "CV%" as used in Tables 4 and 7 in the specification. These terms refer to the variability or reproducibility of the assay results, which is described in terms of the "coefficient of variability" or CV. The CV is expressed as a percentage in this case, so it is identified as "CV%".

The coefficient of variability refers to the standard deviation for a series of measurements of a parameter, divided by the mean value of the parameter: it is a value that is routinely used to express the variability of a quantitative assay. The "intra-assay" value relates to a series of measurements of a parameter (e.g., the sodium level in a sample) that are made during a single determination; the "inter-assay" variability relates to measurements made in separate determinations on a given sample, using the same assay method. Thus the tables quantify the reproducibility of each method's results within a given assay and between assays on a given sample.

As evidence that these terms were well understood in the art when the application was filed, the applicant provides a reference by Reed, et al., entitled "Use of Coefficient of Variation in Assessing Variability of Quantitative Assays", Clinical and Diagnostic Laboratory Immunology, vol. 9(6), 1235-59 (2002), which is attached hereto as **Exhibit A,** and is available online at the following URL: www.pubmedcentral.nih.gov/picrender.fcgi?artid=130103&blobtype=pdf.

Next, the Examiner asserted that the specification does not teach which 3'(2')5'-bisphosphate nucleotidases are sodium-sensitive, and which are lithium-sensitive, so one of ordinary skill would not have known how to practice the invention. However, the specification provides numerous references that describe the ion sensitivities of suitable phosphatase enzymes:

Lopez-Coronado (J. Biol. Chem. 274(23), 16034-39 (1999), cited at paragraph [0040] of the specification) describes RnPIP, which has PAP phosphatase activity that "was not affected by high Na+ concentrations, whereas it was very sensitive to Li+ (0.8 mM LiCl for 50% inhibition at 0.2 mM PAP)" (Lopez-Coronado at pg. 16037, right col.).

Gil-Mascarell, et al., The Plant Journal 17(4), 373-83 (1999), also cited in paragraph [0040] of the specification, describes an Arabidopsis PAP phosphatase referred to as AHL that is sensitive to both sodium and lithium, but is particularly sensitive to sub-physiological levels of Na+, having an IC-50 of 50 mM for Na+. (Gil-Mascarell at pg. 378, left col.) (Normal physiological levels of Na+ are about 135-145 mM: specification at para. [0002].)

Miyamoto, et al. (J. Bacteriol. 182(13), 3619-25 (2000) describes a 3'(2'),5'-bisphosphate nucleotidase that is sensitive to sodium, but about 100 fold more sensitive to lithium. (Miyamoto is cited in the specification at paragraph [0040], but the author's name is incorrect, and corrected by the present amendment). See Fig. 3 in Miyamoto, at page 3621.

Peng, et al., J. Biol. Chem. 270(49), 29105-10 (1995) also cited in paragraph [0040], describes a rice-derived homolog of HAL2 called RHL, which was inhibited by both sodium and lithium with Ki = 0.85 mM Li+ and 55 mM Na+. However, "inhibition by Na+ was eliminated by elevated K+." (Peng at pg. 29108, left col.) Accordingly, lithium could be measured in a sample having elevated K+ to relieve the effect of Na+ present.

Moreover, the application identifies at least one suitable example of a chimeric protein, the protein of SEQ ID NO:4, in paragraph [0050]. That protein was claimed by its sequence in original claim 23, and is thus fully described and is singled out as a suitable protein for use in the claimed methods. The application also cites experimental examples using a chimeric protein to measure both lithium levels (Example 2, paragraphs [00121]-[00123]) and sodium levels (Example 1, paragraphs [00112]-[00114]), and it discloses the lithium sensitivity and the sodium sensitivity of the protein. The peptide of SEQ ID NO: 4 is the same peptide used in Examples 1 and 2, as is shown by the Declaration by Dr. Yuan, which accompanies this response, and is identified as

Exhibit B. Dr. Yuan's curriculum vitae is attached as **Exhibit C**. Accordingly, that peptide is useful for methods to determine both sodium and lithium concentrations.

The application thus provides sufficient guidance to the relevant information to allow one of ordinary skill to identify suitable enzymes with which to practice the invention. It identifies one such protein by sequence, and the necessary information about others was well known in the art before the application was filed. In addition, the references demonstrate that one can readily determine the sodium and/or lithium sensitivities of proteins for use in the methods; thus one can readily ascertain whether chimeric forms of such proteins exhibit sensitivity to lithium or sodium, using methods that are routine in the art. Accordingly, one of ordinary skill would be able to practice the invention without undue experimentation using the guidance provided in the specification and the knowledge generally available in the art.

The Examiner indicated that an enzyme presumably must be sensitive to one or the other of sodium and lithium, but not to both, in order for the assay method to be useful. The applicant notes, however, that this assumption is not necessarily correct. For example, an assay sensitive to both would be useful for analyzing lithium levels in a 'normal' human clinical sample, as long as its sensitivity to sodium was low enough so that 'normal' levels of sodium (135-145 mM according to the specification at paragraph [0002]) would not interfere with measuring a lithium concentration. Similarly, an assay sensitive to both sodium and lithium would be useful to measure sodium in samples where lithium is known <u>not</u> to be present in amounts that would interfere with measuring normal levels of sodium, or where sensitivity to lithium is sufficiently low relative to that of sodium so that it would not interfere within that range. Since lithium is not typically present in significant quantities in clinical samples unless the patient is taking lithium as a medication, and is never present in levels comparable to normal sodium levels due to its toxicity, the assay would be useful for most samples even if the enzyme were sensitive to both sodium and lithium. The Declaration by Dr. Yuan further supports the conclusion that a peptide need not be specific for either lithium or sodium in order to be used successfully in the claimed methods, even in a sample that contains both ions. And, of course, the claimed methods may be useful for determinations of lithium and/or sodium in samples where only one ion is present, or for determination of one where the level of the

other is already known. Accordingly, the nucleotidase or other protein need not be sensitive to only one of the two ions in order for the assay to be functional and useful.

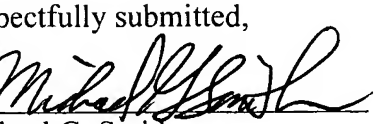
The Examiner also inquired about the purpose of the leader sequence of the chimeric protein. The chimeric proteins are suitable for use in the claimed methods, and are the preferred mode as disclosed; advantages of the chimeric proteins that contain a bacterial leader sequence (stability, easier purification) are provided at paragraph [0034] of the specification, for example. However, it is unclear how this inquiry relates to any claim rejections, since such proteins are adequately described and enabled, so further clarification appears unnecessary.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 466992001100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 29, 2006

Respectfully submitted,

By 

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